THE MEDICAL LETTER

a non-profit publication

on Drugs and Therapeutics

Published by Drug and Therapeutic Information, Inc., 305 East 45th Street, New York 17, New York

Vol. 3, No. 24 (Issue #75) November 24, 1961

CAPLA

A new member has been added to the meprobamate family with the introduction of mebutamate (Capla — Wallace). Mebutamate differs from meprobamate (Miltown — Wallace; Equanil — Wyeth) only in possessing one additional methyl group. Just as a previous change in the meprobamate molecule was claimed to transform the tranquilizer into a highly effective muscle relaxant [carisoprodol (Soma — Wallace; Rela — Schering)], so the new change is claimed to make of the drug a "centrally-acting antihypertensive agent." (See page 94 of this issue for a discussion of meprobamate and carisoprodol as muscle relaxants.)

Large intravenous doses of Capla can produce a fall in blood pressure in animals made hypertensive by desoxycorticosterone or by partial occlusion of the renal arteries. Like barbiturates the drug also reduces the hypertensive response to electrical stimulation of the hypothalamus or medulla (M. Kletzkin and F. M. Berger, Fed. Proc., 20:113, 1961). The relation of these findings to any effects in human essential hypertension is not clear. Capla does not counteract the hypertensive effects of injected epinephrine or norepinephrine, nor does it have any blocking effect on the sympathetic ganglia or on the neuromuscular junction in the blood-vessel wall.

CLINICAL STUDIES - Few reports on the use of Capla to treat human hypertension have been published. In one study, 20 patients with essential hypertension (pretreatment blood pressures greater than 150/100) were treated with Capla. A reduction to 150/90 or of more than 20 mm. Hg in mean arterial pressure (diastolic pressure plus one third of the pulse pressure) was observed in the upright position in only six patients (30 per cent) and in the recumbent position in only four of the patients (C. Duarte, et al., Curr. Ther. Res., 2:148, 1960). This limited effect might be expected with any mild sedative.

Doses up to 1200 mg. daily were used in this study. With such dosage, eight of the patients (40 per cent) complained of drowsiness; it should be noted that this side effect was almost as frequent as the therapeutic effect. Side effects other than drowsiness, each reported as appearing in 10 to 20 per cent of patients, included headache, dry mouth, nasal congestion, constipation, and orthostatic weakness. A more reliable antihypertensive response was seen in patients who received mebutamate with hydrochlorothiazide, but the hypotensive effect of the diuretic alone was not studied.

EDITORIAL BOARD: **Harold Aaron, M.D.**; **Lytt I. Gardner, M.D.**, Prof. of Pediatrics, State Univ. of N. Y., Upstate Medical Center; **Nicholas M. Greene, M.D.**, Prof. of Anesthesiology and Lecturer in Pharmacology, Yale Univ. Med. School; **Paul H. Lavietes, M.D.**, Assoc. Clin. Prof. of Med., Yale Univ. Med. School; *ADVISORY BOARD:* **Louis C. Lasagna, M.D.**, Assoc. Prof. of Med. and Director, Div. of Clin. Pharmacology, Johns Hopkins Med. School; **Desmond R. Laurence, M.D.**, Lecturer in Pharmacology, Univ. Coll. Hosp. Med. School, London; **George E. Moore, M.D.**, Assoc. Prof. of Surgery, Buffalo Univ. Med. School and Director, Roswell Park Memorial Inst.; **John T. Murphy, Phm.D.**, Director of Pharmaceutical Research and Development, Mass. General Hospital; **Maxwell M. Wintrobe, M.D.**, Prof. and Head of Dept. of Med., Univ. of Utah Coll. of Med; **Robert I. Wise, M.D.**, Prof. and Head of Dept. of Med., Jefferson Med. Coll.; *MANAGING DIRECTOR:* **Arthur Kallet.**

Copyright 1961, Drug and Therapeutic Information, Inc.

In a double-blind study (T. Bodi, et al., Am. J. Med. Sci., 239:207, 1960), a 400-mg. dose of Capla was found to be effective as a hypnotic. In fact, the authors state that Capla "differs from meprobamate in having more pronounced hypnotic activity." Except for its sedative effects, Capla cannot be considered an antihypertensive drug; as a sedative, it has no known advantages over older and probably safer drugs.

KEY-PYRONE

Key-Pyrone, a brand of dipyrone recently introduced in oral form by the Key Pharmacal Company, comes on the market at a time when most authorities either question the wisdom of using dipyrone or any other congener of aminopyrine as an analgesic and antipyretic or state flatly that these drugs should not be used (Medical Letter, 3:44, May 26, 1961). The Study Group on Blood Dyscrasias of the Council on Drugs of the American Medical Association in its 1960 report lists 11 cases of leukopenia associated with dipyrone.

Since much safer analgesics and antipyretics such as aspirin are available, Medical Letter consultants feel that there are practically no circumstances in which this drug is indicated. (Phenacetin and acetaminophen are probably safer than dipyrone in patients who cannot tolerate aspirin.) The manufacturer recommends dosages as high as 8 grams a day (four 500-mg. tablets four times a day) for adults.

The warnings in the manufacturer's literature are inadequate, for example: "Should the patient experience this type of side effect ['rash, edema or an individual idiosyncrasy to the medication'], dosage should be temporarily discontinued or reduced." (Our emphasis.)

MUSCLE RELAXANTS — II.

(A general appraisal of drugs offered as muscle relaxants appeared in the November 10th issue of The Medical Letter. The following notes on the various agents complete the discussion of this group of drugs.)

MEPROBAMATE (Miltown — Wallace; Equanil — Wyeth), like carisoprodol, methocarbamol, and mephenesin, is a substituted propanediol; it is claimed to provide muscle-relaxant action which is independent of its sedative or tranquilizing properties. Despite the extensive literature supporting its usefulness as a relaxant, there is no acceptable evidence that it has effects which are independent of its sedative action. Parenteral, but not oral, administration can provide a clinically useful, although brief, relaxant effect.

CARISOPRODOL (Soma — Wallace; Rela — Schering), an isopropyl analogue of meprobamate, is claimed not only to be a muscle relaxant, but also to possess "unusual analgesic properties" in inflammatory, traumatic, degenerative and congenital disorders associated with muscle spasm, tension and pain. Most of the reports favoring the use of this drug were based on the clinical impressions de-

rived from a series of uncontrolled studies (Ann. N. Y. Acad. Sci., 86:1-310, 1960; The Pharmacology and Clinical Usefulness of Carisoprodol, Wayne State Univ. Press, 1959). In one of the few controlled trials included in the Wayne State University Press series (D. R. Korst, et al., p. 104), neither carisoprodol nor a placebo caused a significant change in the spasticity of chronic neurologic disorders. In a controlled study of 34 patients with temporomandibular joint pain and spasm of the facial muscles, pain and spasm were relieved in five patients on carisoprodol, but the placebo was also effective in five patients, and the remaining 24 patients showed no improvement with either the drug or the placebo (L. Schwartz, et al., Ann. N. Y. Acad. Sci., cited above, p. 245).

In a double-blind crossover study with cerebral palsy patients (E. Denhoff and R. H. Holden, N. E. J. Med., 264:475, 1961), over-all improvement was noted in only two of 10 children on carisoprodol; of six children with spasticity, all were rated as unchanged or worse. Of eight of these patients given placebo, six showed over-all improvement.

As for the analgesic effects of the drug, two reports on its effects in experimentally-induced pain indicated that it was superior to aspirin (A. R. Holliday and J. M. Dille, Ann. N. Y. Acad. Sci., cited above, p. 147; S. Margolin, Proc. Soc. Exper. Biol. & Med., 105:531, 1960). A clinical study on postoperative pain indicated that the analgesic effects of carisoprodol in this condition were no greater than those of a placebo (R. Adams and R. Holden, Ann. N. Y. Acad. Sci., cited above, p. 233).

METHOCARBAMOL (Robaxin — Robins), a 3-ortho-methoxy derivative of mephenesin, is claimed to exert "a prolonged blocking activity on multisynaptic reflexes without significantly affecting monosynaptic reflexes," and to decrease "skeletal muscle spasm and pain." It is available in both oral and parenteral forms. All of the clinical studies on Robaxin thus far reported were uncontrolled. Like the barbiturates and other sedative agents, the parenteral form of the drug probably has a brief effect in relieving severe muscle spasm and in producing muscle relaxation to facilitate manipulation of dislocated joints. If oral Robaxin has greater muscle-relaxant effect than barbiturates or tranquilizers or greater analgesic effect than aspirin, it is unfortunate that there are no well-controlled trials to prove it. Among the side effects are drowsiness, weakness, gastrointestinal disturbances, dry mouth, headache, nausea and occasional skin rash.

CHLORMEZANONE (Trancopal — Winthrop) is a metathiazanone, unrelated to other muscle relaxants, tranquilizers or analgesics in current use. Like other muscle relaxants, however, it is offered for the relief of muscle spasm and spasticity associated with muscular and neurological disorders, and it is also claimed to have tranquilizing activity. Neither in experimental animals nor in man has the drug shown any effect on the skeletal muscle or on the myoneural junction; whatever clinical effects it has appear to result from its central-nervous-system tranquilizing action.

One controlled trial of Trancopal (F. Torres, et al., Minn. Med., 43:16, 1960) involved a three-month study of 10 adult patients with multiple sclerosis and spasticity of the lower extremities (five had been treated earlier with zoxa-

zolamine, mephenesin and quinine without sustained improvement). The drug had a mild tranquilizing-sedative effect but there was no significant difference between the active drug and the placebo in effect on spasticity. Another study showed no significant effect on spasticity in seven children with cerebral palsy (four were given 100 mg. of Trancopal three times a day for a period of six weeks; three were given placebos) (H. M. Sterling, Arch. Phys. Med., 41:226, 1960). The side effects reported so far are mild, consisting of occasional drowsiness, nausea, skin eruptions, dizziness, headache, dry mouth, flushing, and loss of appetite. Since all studies have been short-term (weeks or months), the full range, severity and frequency of toxic symptoms and other untoward effects of long-term use of the drug are unknown.

PHENYRAMIDOL HYDROCHLORIDE (Analexin — Irwin, Neisler) is a pyridylamine drug which was originally promoted as both an analgesic and a muscle relaxant, "the first analgomylaxant... the only single chemical that raises the pain threshold and relaxes muscle tension simultaneously." No special relaxant effects have been demonstrated, and it is now being promoted as "four hundred milligrams of pure pain relief," with the statement that "the only significant response is relief from pain."

STYRAMATE (Sinaxar — Armour) is a carbamate drug unrelated, however, to derivatives of mephenesin. It is claimed to have "...only one action... 'pure' skeletal muscle relaxant" without tranquilizing properties. The four clinical trials of the drug so far published were all uncontrolled, and none indicated specific muscle-relaxant properties. Some relief of pain was reported in all of these studies, with nausea and weakness as the only side effects.

CHLORZOXAZONE (Paraflex — McNeil) is 5-chlorobenzoxazolinone, a metabolic derivative of zoxazolamine (Flexin — McNeil) but without the latter's uricosuric properties. Unlike the parent substance, Paraflex is promoted exclusively as a "skeletal muscle relaxant" for a wide range of acute and chronic inflammatory, traumatic and degenerative disorders ranging from acute back disorders to wry-neck and chronic neurologic spastic disorders.

Enthusiastic reports on Paraflex have been published, but no effort was made in the studies to check the validity of the observations by controlled trials of the drug in comparison with a placebo and a barbiturate or a tranquilizer. Since spasticity often fluctuates spontaneously, particularly in response to emotional states, valid conclusions cannot be drawn without such controls. Many of the patients in the uncontrolled studies reported side effects, the most common being abdominal distress, nausea, weakness, diarrhea and dizziness. (For a discussion of Flexin, which was recently withdrawn from the market because of its toxicity, see The Medical Letter, 3:86, Oct. 27, 1961.)

In summary, placebos given for muscle relaxation appear to be effective in many patients; some of the drugs sold as muscle relaxants appear to be effective sedatives with no specific muscle-relaxing action. Intravenous administration of a barbiturate, mephenesin or other central-nervous-system-depressing drug does have a moderate though brief effect on muscle spasm, an effect which can, on occasion, be useful.

THE MEDICAL LETTER ON DRUGS AND THERAPEUTICS is published fortnightly by Drug and Therapeutic Information, a non-profit corporation, 305 E. 45th St., New York 17. Second-class postage paid at New York, and at Marion, Ohio. Subscription: 1 yr., $12.50; 2 yrs., $23; 3 yrs., $34 ($6.25 per year for residents, interns, students).